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MAJOR ARTICLE

Comparison of the Effectiveness of Trivalent Inactivated Influenza Vaccine and Live, Attenuated Influenza Vaccine in Preventing Influenza-Like Illness Among US Military Service Members, 2006–2009

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Background. Influenza is a significant cause of morbidity, and vaccination is the preferred preventive strategy. Data regarding the preferred influenza vaccine type among adults are limited.

Methods. The effectiveness of 2 currently available influenza vaccines LAIV and TIV in preventing influenza-like illness (ILI) was compared among US military members (aged 18–49 years) during 3 consecutive influenza seasons (2006–2009). ILI, influenza, and pneumonia events post-vaccination were compared between vaccine types using Cox proportional hazard models adjusted for sociodemographic factors, occupation, and geographic area.

Results. A total of 41 670 vaccination events were evaluated, including 28 929 during 2 "well-matched" seasons (2006–2007 and 2008–2009: LAIV n = 22 734, TIV n = 6195) and 12 741 during a suboptimally matched season due to mild antigenic drift (2007–2008: LAIV n = 9447, TIV n = 3294). ILI crude incidence rates for LAIV and TIV were 139 and 127 cases per 1000 person-seasons for the well-matched seasons, respectively, and 150 and 165 cases per 1000 person-seasons for the suboptimally matched season, respectively. In the multivariable models, there were no differences in ILI events by vaccine type (well-matched seasons: hazard ratio [HR], 0.97; 95% confidence interval [CI], .90–1.06; suboptimally matched season: HR, 1.00; 95% CI, .90–1.11). There were also no differences in influenza and/or pneumonia events by vaccine group.

Conclusions. Between 2006 and 2009, TIV and LAIV had similar effectiveness in preventing ILI and influenza/pneumonia events among healthy adults.

Keywords. pneumonia; influenza-like illness; trivalent inactivated influenza vaccine; attenuated influenza vaccine; military.

Influenza is a significant cause of morbidity and mortality, with approximately 36 000 deaths and 226 000 hospitalizations annually in the United States [1, 2]. Additionally, influenza contributes to significant lost work days each year, impacting both economic productivity and military force readiness [3, 4]. Vaccination is currently the preferred strategy for the prevention of influenza [5, 6].

In the United States, 2 types of influenza vaccines are available: a live, attenuated influenza vaccine (LAIV) and a trivalent inactivated influenza vaccine (TIV). Vaccine efficacy varies by characteristics of the host (eg, age, underlying immunosuppressive conditions) and the vaccine (eg, the similarity, or "match," between the vaccine and circulating strains). The type of influenza vaccine (LAIV, TIV) may also impact the efficacy in preventing influenza and influenza-like

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illness (ILI). In children and adolescents (aged 6 months–18 years), LAIV has been shown to be superior to TIV in several studies [7–9], and in a meta-analysis [10] LAIV was shown to be superior to TIV in preventing both ILI and culture-proven influenza [11, 12]. However, results have been variable among adults, depending on the season and population studied, and several studies did not adequately control for potential confounders [13–19].

Because the Advisory Committee on Immunization Practices (ACIP) currently recommends annual influenza vaccination for all adults regardless of underlying medical conditions [6], it is critical to determine the most effective vaccine type for adults. To provide information on the preferred vaccine among healthy adults, we performed a study comparing LAIV with TIV on ILI and influenza/pneumonia events among US military members during 3 consecutive influenza seasons.

METHODS

Study Population

We conducted a retrospective cohort study among US military members who were participants in a large Department of Defense (DoD) study on health behaviors (ie, Millennium Cohort Study) [20] and completed a survey within 2 years of the vaccination date. Data from the Millennium Cohort Study were utilized to control for potential confounders, which was a limitation of prior studies [15, 17]. Participants were active-duty members stationed in the contiguous United States at the beginning of the influenza season who had received influenza vaccination during 2006–2009; active-duty members are required to receive annual influenza vaccination, with issuance of TIV or LAIV often based on available supply. Unvaccinated members were excluded due to high vaccine coverage rates and potential uncertainties regarding vaccine status. Nonactive-duty military personnel, deployers, and members stationed on ships or overseas were excluded because these groups may be exposed to influenza subtypes not covered by the vaccine and outcomes of interest may be missed in existing databases. Additionally, military recruits were excluded because this group has unique exposure risks for respiratory illnesses.

Participants were followed from the time of influenza vaccination (administered 1 September–30 November of each season) until the end of the influenza season (19 May 2007, 17 May 2008, and 28 March 2009 given the emergence of the pandemic H1N1 strain), occurrence of an ILI, or censoring event [21, 22]. Individuals were right censored if they deployed or transferred outside the continental United States.

All participants were 18–49 years of age at the time of vaccination because LAIV is limited to adults ≤49 years of age. Exclusion criteria included a medical diagnosis of asthma, chronic bronchitis, emphysema, history of shortness of breath, diabetes mellitus, human immunodeficiency virus (HIV) infection, or pregnancy, because LAIV use may be contraindicated and these conditions may result in suboptimal vaccine responses. The study was approved by the Naval Health Research Center institutional review board.

Study Outcomes

Outcomes were defined a priori and based on healthcare encounter data from military and civilian medical facilities. ILI was chosen as the primary outcome because laboratory testing for influenza virus is not commonly used and because ILI has both medical and occupational significance. An ILI was defined by *International Classification of Diseases*, *Ninth Revision* (ICD-9) codes based on previous studies and shown to be related to culture-confirmed influenza in military service members (079.99, 382.9, 460, 461.9, 465.8, 465.9, 466.0, 486, 487.0, 487.1, 487.8, 490, 780.6, and 786.2) [15, 23]. We also examined secondary outcomes of (1) a diagnosis of influenza (487.0, 487.1, and 487.8) and/or pneumonia (486; because the latter may be a complication of influenza), and (2) diagnosis of influenza. In addition, dispensed anti-influenza medications (ie, oseltamivir, zanamivir, amantadine, or rimantadine) were utilized for the diagnosis of ILI and influenza.

Outcomes were captured starting on the first day of the flu season, and only the first ILI event per participant in each influenza season was used in the analyses. Participants with an event during the current influenza season, but before the receipt of vaccination and those occurring ≤14 days post-vaccination, were excluded from analyses to allow adequate time for development of an immune response. Participants could contribute to more than 1 influenza season if they received vaccine and met the inclusion/exclusion criteria during each season. Three consecutive Northern Hemisphere influenza seasons were evaluated. Seasons 2006–2007 and 2008–2009 were analyzed together due to a reported good match between vaccine and circulating strains, and the 2007–2008 season was analyzed separately because of a suboptimal match that was due to slight antigenic drift [16, 22, 24, 25].

Data Collection

Information on sociodemographic and military-related characteristics were obtained from the Defense Manpower Data Center (DMDC) in Monterey, California. These data included age, sex, self-reported race/ethnicity, marital status, education, service branch, military pay grade (enlisted, officer), duty station (coded into 4 geographic locations), duty occupation, and deployment history. Data on preexisting medical conditions used as exclusion criteria were obtained from the Millennium Cohort Study and medical records. Additionally, the Pharmacy Data Transaction Service was utilized to exclude participants receiving medications for diabetes mellitus or

HIV and to capture anti-influenza medications. Data on tobacco use (defined as both ≥100 cigarettes in a lifetime and use within the last year) and potential alcohol problems (defined as an affirmative answer to 1 or more of the 5 Patient Health Questionnaire alcohol questions) [26] were collected from the Millennium Cohort Study. Type and date of influenza vaccinations were obtained from DMDC. The outcomes of interest (ILI, influenza, pneumonia) were determined by review of the Military Health System Data Repository, which contains all outpatient and inpatient encounters from military treatment facilities and TRICARE network providers.

Statistical Analyses

Descriptive statistics are presented as numbers (percentages) for categorical variables and medians (interquartile range, IQR) for continuous variables. The associations between the covariates and primary outcome were assessed for significance using logistic regression (for categorical variables) and the Wilcoxon rank sum test (for continuous variables). Crude incidence rates of ILI per 1000 persons per season were compared between the LAIV- and TIV-immunized groups. Cox proportional hazard modeling was utilized to evaluate the unadjusted and adjusted risk for the primary study outcome (ILI) by the vaccine type (LAIV, TIV) as well as other covariates of interest (sociodemographic, geographic, and behavioral factors). In order to adjust for the potential effects of individuals contributing to multiple seasons, a robust variance estimator was used. To account for individuals receiving the vaccination at different times in relation to the influenza season, a left truncated model was developed starting with survival time at 1 September of the influenza season and truncating on the date of vaccination plus 14 days. A final multivariable model was derived using a backward, stepwise approach and was adjusted for covariates that were significantly associated with the outcome ($P < .05$) or that confounded the relationship between vaccine type and ILI by ≥10%. In addition, interactions were evaluated between vaccine type and sex, service branch, and influenza season. Results of the Cox models were presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Separate models were created for the (1) "well-matched" seasons (2006–2007 and 2008–2009) and (2) the season with an antigenic drift labeled "suboptimally matched" (2007–2008). Additionally, separate models were created for the secondary outcomes of influenza/pneumonia and influenza. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

RESULTS

Study Population Characteristics

A total of 41 670 vaccination events were evaluated, including 28 929 during 2 "well-matched" seasons (2006–2007 and 2008–2009: LAIV n = 22 734, TIV n = 6195) and 12 741 during a "suboptimally matched" season (2007–2008: LAIV n = 9447, TIV n = 3294). The median age of the cohort was 27 years (IQR, 23–34); 73% were white, 72% male, and 27% were recent tobacco users (Table 1). Regarding vaccine type, LAIV accounted for 79% and 74% of the influenza vaccinations during the well-matched and suboptimally matched seasons, respectively. LAIV recipients were more likely to be younger, smokers, vaccinated in the 2008–2009 season (compared with 2006–2007), or residing outside the US Southwest (all $P < .05$). Those with a potential drinking problem, a bachelor's degree or higher, women, officers, serving in the Navy or Marines (compared with the Air Force), vaccinated in the 2007–2008 season (compared with 2006–2007), or in a healthcare occupation were less likely to have received LAIV (all $P < .05$). Vaccine type did not significantly differ by marital status, race/ethnicity, combat occupations (compared with other occupations), or serving in the Army (compared with the Air Force).

Influenza-Like Illness Events

A total of 5893 ILI events were diagnosed during 2006–2009, for an overall crude ILI incidence rate of 141.1 cases per 1000 persons-season. Weekly data for ILI cases demonstrated a similar pattern to that of positive influenza isolates in the general population using Centers for Disease Control and Prevention (CDC) surveillance data (Figure 1). ILI rates for LAIV and TIV were 138.5 and 127.0 cases per 1000 person-seasons, respectively, during well-matched seasons. In the univariable model during the well-matched seasons, type of vaccine was not significantly associated with the development of an ILI (HR, 1.02; 95% CI, .95–1.11; Table 2). In the final multivariable model adjusted for all significant covariates, the risk of ILI did not significantly differ between LAIV and TIV (HR, 0.97; 95% CI, .90–1.06) (Table 2). Factors associated with an increased risk of ILI included younger age, female sex, recent smoking, 2008–2009 influenza season, and healthcare-related occupation. Black race, unmarried status officer rank, combat occupation, and Army/Marine Corps service branch were associated with a reduced risk (Table 2). We also examined LAIV and TIV for the 2006–2007 and 2008–2009 seasons in separate multivariable models and found no significant associations of ILI events with vaccine type. Finally, stratification by smoking status was performed with similar results (data not shown).

During the suboptimally matched season, the crude ILI rates were 149.6 per 1000 person-season for LAIV recipients and 165.1 per 1000 person-season for TIV recipients. In the univariable and multivariable models, vaccine type was not associated with the risk of ILI (HR, 0.94; 95% CI, .85–1.04 and HR, 1.00; 95% CI, .90–1.11, respectively). Factors significantly

Table 1. Study Population Characteristics and Outcome Data[a] Among US Service Members, 18–49 Years of Age, During 3 Sequential Influenza Seasons (2006–2009)

		Well-Matched Seasons				Suboptimally Matched Season	
		2006–2007		2008–2009		2007–2008	
		Vaccine Type					
Factor	Total	TIV	LAIV	TIV	LAIV	TIV	LAIV
Number of vaccination events	41 670	2905	10 316	3290	12 418	3294	9447
ILI event	5893 (14.1)	383 (13.2)	1477 (14.3)	404 (12.3)	1672 (13.5)	544 (16.5)	1413 (15.0)
Influenza	165 (0.4)	7 (0.2)	16 (0.2)	9 (0.3)	44 (0.4)	28 (0.9)	61 (0.6)
Pneumonia and/or influenza	306 (0.7)	15 (0.5)	47 (0.5)	17 (0.5)	89 (0.7)	40 (1.2)	98 (1.0)
Age, years median (IQR)	27 (23–34)	25 (22–32)	25 (22–33)	28 (24–35)	27 (24–35)	28 (24–36)	26 (23–34)
Race/ethnicity							
White	30 333 (72.8)	2195 (75.6)	7520 (72.9)	2345 (71.3)	9030 (72.7)	2399 (72.8)	6844 (72.4)
Black	5199 (12.5)	286 (9.8)	1305 (12.7)	446 (13.6)	1583 (12.7)	426 (12.9)	1153 (12.2)
Other	3023 (7.3)	206 (7.1)	714 (6.9)	261 (7.9)	896 (7.2)	224 (6.8)	722 (7.6)
Unknown	3115 (7.5)	218 (7.5)	777 (7.5)	238 (7.2)	909 (7.3)	245 (7.4)	728 (7.7)
Sex							
Male	30 189 (72.4)	2046 (70.4)	7537 (73.1)	2241 (68.1)	9179 (73.9)	2160 (65.6)	7026 (74.4)
Female	11 481 (27.6)	859 (29.6)	2779 (26.9)	1049 (31.9)	3239 (26.1)	1134 (34.4)	2421 (25.6)
Service branch							
Air Force	20 129 (48.3)	1168 (40.2)	5469 (53.0)	1215 (36.9)	6439 (51.9)	1656 (50.3)	4182 (44.3)
Army	13 925 (33.4)	651 (22.4)	3639 (35.3)	923 (28.1)	4192 (33.8)	1265 (38.4)	3255 (34.5)
Marine Corps	4422 (10.6)	774 (26.6)	679 (6.6)	651 (19.8)	870 (7.0)	137 (4.2)	1311 (13.9)
Navy	3194 (7.7)	312 (10.7)	529 (5.1)	501 (15.2)	917 (7.4)	236 (7.2)	699 (7.4)
Marital status							
Married	25 863 (62.1)	1605 (55.2)	5847 (56.7)	2233 (67.9)	8172 (65.8)	2096 (63.6)	5910 (62.6)
Other	15 807 (37.9)	1300 (44.8)	4469 (43.3)	1057 (32.1)	4246 (34.2)	1198 (36.4)	3537 (37.4)
Rank							
Enlisted	31 525 (75.7)	2117 (72.9)	7914 (76.7)	2421 (73.6)	9479 (76.3)	2255 (68.5)	7339 (77.7)
Officer	10 145 (24.3)	788 (27.1)	2402 (23.3)	869 (26.4)	2939 (23.7)	1039 (31.5)	2108 (22.3)
Education							
<Bachelor's degree	29 860 (71.7)	2048 (70.5)	7519 (72.9)	2279 (69.3)	8942 (72.0)	2099 (63.7)	6973 (73.8)
≥Bachelor's degree	11 810 (28.3)	857 (29.5)	2797 (27.1)	1011 (30.7)	3476 (28.0)	1195 (36.3)	2474 (26.2)
Occupation							
Other	27 646 (66.3)	1835 (63.2)	7046 (68.3)	2024 (61.5)	8513 (68.6)	1820 (55.3)	6408 (67.8)
Combat	7553 (18.1)	478 (16.5)	1821 (17.7)	542 (16.5)	2390 (19.2)	553 (16.8)	1769 (18.7)
Healthcare	6471 (15.5)	592 (20.4)	1449 (14.0)	724 (22.0)	1515 (12.2)	921 (28.0)	1270 (13.4)
Recent smoking history	11 389 (27.3)	776 (26.7)	2814 (27.3)	941 (28.6)	3424 (27.6)	764 (23.2)	2670 (28.3)
Potential alcohol problem	3228 (7.7)	292 (10.1)	760 (7.4)	274 (8.3)	895 (7.2)	236 (7.2)	771 (8.2)
US geographic area							
Southwest	12 733 (30.6)	1101 (37.9)	2997 (29.1)	1348 (41.0)	3300 (26.6)	1195 (36.3)	2792 (29.6)
Southeast	12 652 (30.4)	966 (33.3)	3322 (32.2)	954 (29.0)	3750 (30.2)	845 (25.7)	2815 (29.8)
Northeast	9466 (22.7)	537 (18.5)	2013 (19.5)	667 (20.3)	3150 (25.4)	895 (27.2)	2204 (23.3)
Northwest	6819 (16.4)	301 (10.4)	1984 (19.2)	321 (9.8)	2218 (17.9)	359 (10.9)	1636 (17.3)

Abbreviations: ILI, influenza-like illness; IQR, interquartile range; LAIV, live, attenuated influenza vaccine; TIV, trivalent inactivated influenza vaccine.

[a] Numbers (percentages) and medians (IQR).

associated with a decreased risk of ILI during this season were male sex, unmarried status, officer rank, and non-Air Force service branches (Table 2).

Given previous reports that younger adults may have varying responses to LAIV and TIV [15, 17], we examined the subgroup of 18- to 24-year-old service members

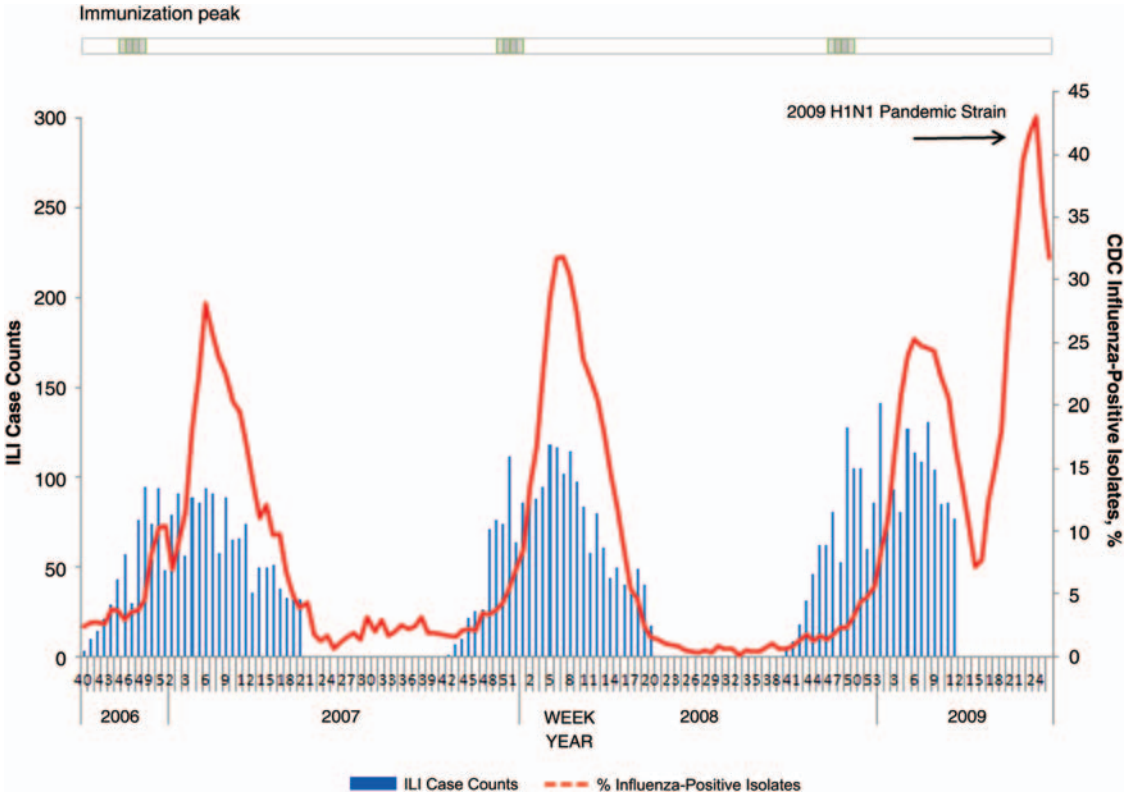

Figure 1. Incident ILI events following influenza vaccination among US military service members, 2006–2009. Influenza-like illness (ILI) events were defined by medical encounters among US military service members (left y-axis) and positive isolates for influenza among the general population were obtained from the Centers for Disease Control and Prevention (right y-axis). Due to the novel 2009 H1N1 pandemic strain, ILI events end in March of 2009. The upper gray bar represents immunization peak period for each season. Abbreviations: CDC, Centers for Disease Control and Prevention; ILI, influenza-like illness.

(n = 10 212) during the well-matched seasons. In the final multivariable model (adjusted for all covariates), there was no significant association with type of influenza vaccine and ILI events (HR 1.09 for LAIV compared with TIV; 95% CI, .95–1.25).

Influenza and Pneumonia Events

A total of 168 cases of influenza and/or pneumonia were noted during the well-matched seasons, with a crude rate of 6.0 and 5.2 per 1000 person-seasons for LAIV and TIV recipients, respectively. In the final Cox proportional hazards model, the risk for influenza/pneumonia was not significantly different between vaccine groups (HR, 1.15; 95% CI, .78–1.69; Table 3). Factors associated with influenza/pneumonia included female sex (HR, 1.67; 95% CI, 1.22–2.29) and 2008–2009 season (HR, 1.73; 95% CI, 1.23–2.44), whereas unmarried status was associated with a lower risk (HR, 0.62; 95% CI, .44–.87).

There were 138 events during the suboptimally matched season, with crude rates of 10.4 and 12.1 per 1000 person-seasons among LAIV and TIV recipients, respectively. In the final model, vaccine type was not associated with influenza/pneumonia (HR, 0.87; 95% CI .60–1.27); the only significant factors were Army (HR, 0.60; 95% CI, .40–.88) and Navy (HR, 0.37; 95% CI .15–.91) personnel having a lower risk compared with Air Force personnel (Table 3).

There were 76 influenza cases during the well-matched seasons, with a crude rate of 2.6 cases per 1000 person-seasons among both LAIV and TIV recipients. In the final multivariable model, vaccine type was not associated with influenza events (HR, 0.98; 95% CI .56–1.72). Likewise, during the suboptimally matched season, the rate of influenza was 6.5 and 8.5 cases per 1000 person-seasons for LAIV and TIV recipients, respectively, and there was no association in the final model (HR, 0.79; 95% CI .50–1.24; Table 3).

DISCUSSION

Our multiseason study found that LAIV and TIV had similar overall effectiveness against ILI and influenza/pneumonia events during 2006–2009. These data suggest that healthy adults achieve similar protection from both vaccine types and

Table 2. Univariable and Multivariable Models of Risk of ILI Events Among US Service Members, 18–49 Years of Age, During Well-Matched (2006–2007 and 2008–2009) and Suboptimally Matched (2007–2008) Seasons

	Well-Matched Seasons		Suboptimally Matched Season	
Factor	Univariable Analyses HR (95% CI)	Multivariable Analysis HR (95% CI)	Univariable Analyses HR (95% CI)	Multivariable Analysis HR (95% CI)
Vaccine type, LAIV	1.02 (.95–1.11)	0.97 (.90–1.06)	0.94 (.85–1.04)	1.00 (.90–1.11)
Age, per year	0.99 (.98–.99)*	0.99 (.986–.997)*	0.99 (.99–.998)*	—
Race/ethnicity				
White	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	—
Black	1.00 (.91–1.10)	0.89 (.80–.98)*	1.03 (.90–1.17)	
Hispanic	1.08 (.95–1.22)	1.06 (.93–1.20)	1.07 (.91–1.27)	
Other/unknown	1.17 (1.04–1.32)*	1.10 (.98–1.24)	1.08 (.91–1.27)	
Sex, female	1.84 (1.72–1.96)*	1.71 (1.59–1.83)*	1.75 (1.60–1.91)*	1.72 (1.57–1.89)*
Service branch				
Air Force	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Army	0.74 (.68–.79)*	0.78 (.72–.84)*	0.76 (.69–.84)*	0.80 (.72–.88)*
Marine Corps	0.43 (.37–.50)*	0.47 (.40–.55)*	0.53 (.45–.64)*	0.60 (.50–.72)*
Navy	0.90 (.80–1.02)	0.89 (.79–1.00)	0.77 (.64–.91)*	0.77 (.64–.91)*
Marital status, unmarried	1.02 (.96–1.09)	0.89 (.83–.96)*	0.96 (.87–1.05)	0.85 (.77–.93)*
Military rank, officer	0.77 (.71–.84)*	0.80 (.73–.87)*	0.73 (.65–.81)*	0.71 (.63–.79)*
Occupation				
Other	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)	—
Combat	0.76 (.69–.84)*	0.89 (.81–.98)*	0.77 (.68–.88)*	
Healthcare	1.28 (1.18–1.39)*	1.10 (1.01–1.21)*	1.17 (1.05–1.31)*	
Recent smoking history	1.09 (1.02–1.17)*	1.10 (1.02–1.18)*	1.07 (.97–1.18)	—
Potential alcohol problem	0.90 (.79–1.02)	—	0.75 (.62–.90)*	—
US geographic area				
Southwest	1.00 (Ref)	—	1.00 (Ref)	—
Southeast	0.98 (.90–1.06)		1.01 (.90–1.14)	
Northeast	0.92 (.84–1.00)		1.04 (.92–1.17)	
Northwest	1.04 (.95–1.15)		0.95 (.83–1.10)	
Influenza season, 2008–2009	1.07 (1.00–1.14)*	1.08 (1.01–1.15)*	NA	NA

—Designates that the variable was not significant in the final multivariable model.

Abbreviations: CI, confidence interval; HR, hazard ratio; ILI, influenza-like illness; LAIV, live, attenuated influenza vaccine; NA, not applicable.

*$P < .05$.

support the current ACIP recommendations for influenza vaccination among this population.

The most important step in reducing influenza-related morbidity and mortality in a population is to ensure vaccination [6]. An additional consideration is the type of vaccine to use in specific populations. Although several studies have demonstrated the superior efficacy of LAIV compared with TIV in children and adolescents [7–12], there is no consensus regarding the most efficacious vaccine type among adults. Currently, decisions regarding vaccine type among adults are often based on supply and preferences regarding administration route and potential side effects [27]. For example, LAIV has increasingly been utilized by the US military due to its relative ease of administration and ample supply [17]. The current US military recommendations regarding influenza vaccination notes that either LAIV or TIV may be used among adults without contraindications to LAIV, which are similar to ACIP recommendations [6, 28]. Data on the most effective type of influenza vaccination is paramount to ensure a healthy and fit population and military force and to inform DoD and other agencies about the optimal influenza vaccine type among healthy adults.

Our study found that LAIV and TIV had similar rates of ILI, influenza/pneumonia, and influenza events. A prior study using existing medical records of US military personnel during earlier influenza seasons (2004–2007) found that TIV offered more protection from influenza and/or pneumonia (diagnosed using ICD-9 codes) than did LAIV [17]. A second

Table 3. Final Multivariable Models of Risk of Influenza/Pneumonia and Influenza Events Among US Service Members, 18–49 Years of Age, During Well-Matched (2006–2007 and 2008–2009) and Suboptimally Matched (2007–2008) Seasons

	Influenza and/or Pneumonia Events		Influenza Events	
Factor	Well-Matched Seasons HR (95% CI)	Suboptimally Matched Season HR (95% CI)	Well-Matched Seasons HR (95% CI)	Suboptimally Matched Season HR (95% CI)
Vaccine type, LAIV	1.15 (.78–1.69)	0.87 (.60–1.27)	0.98 (.56–1.72)	0.79 (.50–1.24)
Age, per year	—	—	1.03 (1.00–1.07)*	—
Sex, female	1.67 (1.22–2.29)*	—	2.86 (1.82–4.49)*	—
Service branch				
Air Force	—	1.00 (Ref)	1.00 (Ref)	1.00 (Ref)
Army		0.60 (.40–.88)*	0.52 (.30–.91)*	0.45 (.27–.75)*
Marine Corps[a]		0.78 (.45–1.37)	0.44 (.14–1.45)	0.63 (.29–1.33)
Navy[a]		0.37 (.15–.91)*	0.29 (.09–.94)*	0.31 (.10–.99)*
Marital status, unmarried	0.62 (.44–.87)*	—	—	0.55 (.34–.89)*
Influenza season, 2008–2009	1.73 (1.23–2.44)*	NA	2.20 (1.30–3.71)*	NA

—Designates that the variable was not significant in the final multivariable model.

Abbreviations: CI, confidence interval; HR, hazard ratio; LAIV, live, attenuated influenza vaccine; NA, not applicable.

* $P < .05$.

[a] Some data with <10 outcomes.

study in military members found that nonrecruits who received TIV had lower rates of ILI, whereas LAIV was more effective among recruits [15]. However, these studies did not control for several important confounders (tobacco use, occupation, or geographic area) and utilized different methodologies to select their study populations. For example, we excluded persons outside the contiguous United States (eg, Navy afloat, service members receiving sea pay, and those vaccinated while deployed) as these populations are more likely to receive TIV (rather than LAIV) and less likely to have medical events recorded in the electronic data files (confirmed using data from the medical data repository and DMDC). We reanalyzed our data without these exclusions and found estimates similar to those from prior studies [15, 17], suggesting that deployers and personnel at sea may have influenced prior results regarding TIV's effectiveness. Regarding the general population, randomized, placebo-controlled studies on university campuses in Michigan showed that TIV was either similarly or more efficacious than LAIV [13, 14, 16]. Our study adds important data to the literature by providing robust population-based data that was controlled for many potential confounders (obtained from both medical/military records and participant questionnaires) and encompassed 3 sequential seasons. Our study suggests that among healthy adults without significant comorbidities, vaccine type is not a differentiating factor for ILI and influenza/pneumonia events during the influenza season. Overall, these data suggest that adults can be vaccinated with either vaccine type, which potentially simplifies vaccination protocols and focuses attention on the key factor of ensuring vaccination itself.

The reasons for the potential varying effectiveness of vaccine types based on the population (children compared with adults) may be the result of the divergent immune responses elicited. TIV is administered intramuscularly with rapid introduction into the bloodstream and induction of serum antibodies, whereas the intranasal administration of LAIV induces both humoral (serum and mucosal immunoglobulin A antibodies) and cell-mediated immune responses [29, 30]. As such, LAIV may be superior as a priming vaccine among young persons (eg, aged <18 years and perhaps young military recruits) who have little preexisting immunity [17]. As a boosting vaccine, TIV's efficacy is higher in adults relative to children (likely due to preexisting immunity), resulting in its comparable effectiveness seen in adults.

In our study, the impact of ILI/influenza events was substantial—14% of this healthy well-vaccinated adult population had a medical visit for an ILI and 0.7% for influenza/pneumonia during each season. The economic burden of all influenza events in the United States is an estimated $87 billion per year due to work absenteeism, healthcare-associated costs, and premature mortality [3, 31]. Even among healthy adults aged 18–49 years without predisposing medical conditions (similar to our population), influenza causes millions of healthcare visits each year [31]. Additionally, among military members, such events may have implications for national security [4, 32].

Our study has some limitations. The study's outcomes were based on ICD-9 codes, rather than culture- or polymerase chain reaction–confirmed influenza; however, ICD-9 codes previously have been correlated with influenza events [15, 17, 23]. Our study focused on ILI events requiring a medical visit and did not capture outcomes for which the participant did not seek care. Given our young, healthy population, the number of confirmed influenza and/or pneumonia events was small; hence, we may have missed potential associations for these outcomes. However, our primary model had a power of 80% to detect an HR as low as 1.13. Data collected from military records and participant questionnaires may be subject to misclassification errors and reporting biases, but these were likely nondifferential in nature. Finally, our study focused on a highly vaccinated population of healthy adults and did not evaluate high-risk adults such as those aged ≥50 [19] or with immunocompromising conditions (eg, HIV, diabetes, pregnancy). More research on the preferred vaccine in these populations and adults with negative health behaviors (eg, alcohol and smoking) is needed.

In summary, recommendations for influenza vaccination have recently expanded to include all adults. Our study demonstrated that LAIV and TIV have similar efficacy in preventing ILI and influenza/pneumonia events among healthy 18- to 49-year-olds. These data provide valuable information for providers and policy makers regarding the influenza vaccination among healthy adults.

Notes

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14. ABSTRACT

Influenza is a significant cause of morbidity, and vaccination is the preferred preventive strategy. Data regarding the preferred influenza vaccine type among adults are limited. The effectiveness of 2 currently available influenza vaccines [live, attenuated influenza vaccine (LAIV) versus trivalent inactivated influenza vaccine (TIV)] in preventing influenza-like illness (ILI) were compared among US military members (aged 18–49 years) during 3 consecutive influenza seasons (2006–2009). ILI, influenza, and pneumonia events post-vaccination were compared between vaccine types using Cox proportional hazard models adjusted for sociodemographic factors, occupation, and geographic area. A total of 41,670 vaccination events were evaluated, including 28,929 during 2 "well-matched" seasons (2006–2007 and 2008–2009; LAIV *n* = 22,734, TIV *n* = 6195) and 12,741 during a "poorly matched" season (2007–2008; LAIV *n* = 9447; TIV *n* = 3294). ILI incidence rates for LAIV and TIV were 139 and 127 cases per 1000 person-seasons for the well-matched seasons, and 150 and 165 respectively, for the poorly matched season. In the multivariable models, there were no differences in ILI events by vaccine type (well-matched seasons: hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.90–1.06; poorly matched: HR, 1.00; 95% CI, 0.90–1.11). There were also no differences in influenza and/or pneumonia events by vaccine group. Between 2006–2009, TIV and LAIV had similar effectiveness in preventing ILI and influenza/pneumonia events among healthy adults

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